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Palladium-Catalysed Cross-Coupling of Benzylammonium Salts with Boronic Acids under Mild Conditions

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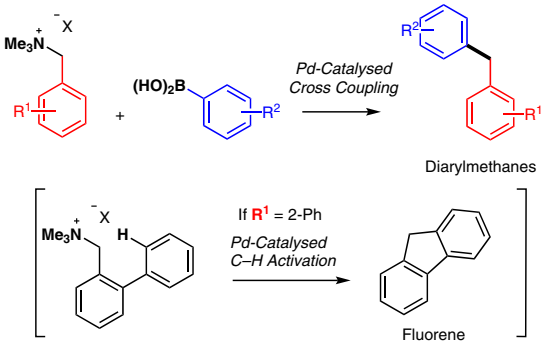
Published as part of the Bürgenstock Special Section 2017 *Future Stars in Organic Chemistry*



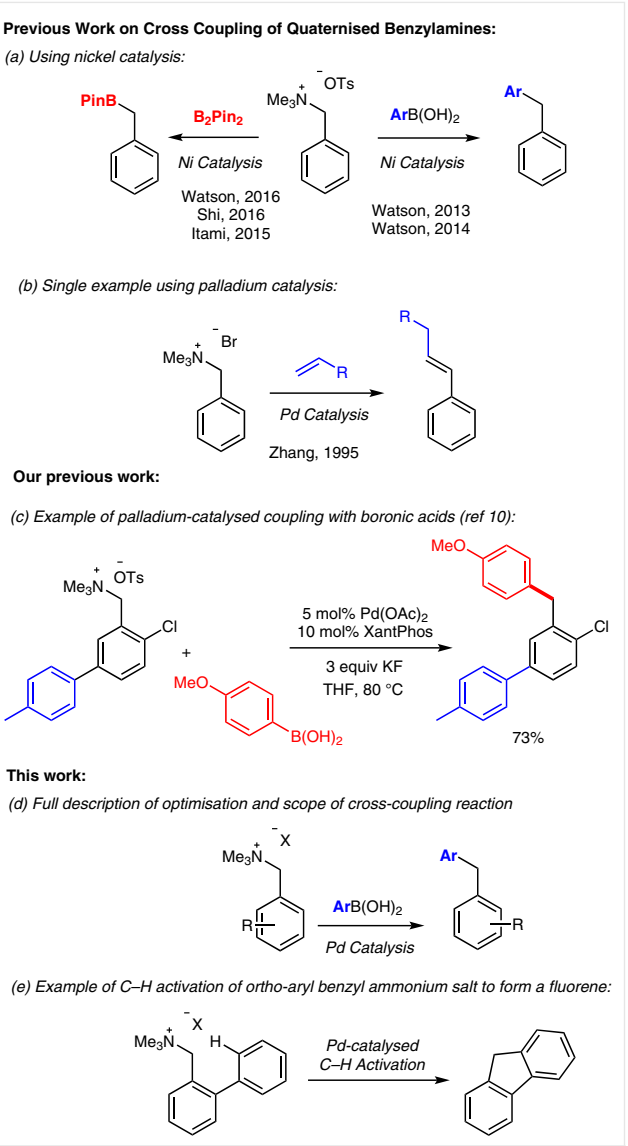
Received: 15.06.2017
Accepted after revision: 20.07.2017
Published online: 23.08.2017
DOI: 10.1055/s-0036-1588548; Art ID: ss-2017-z0402-op

Abstract Herein, we give a full account of the development of the palladium-catalysed cross-coupling of benzylammonium salts with boronic acids. A range of benzylamine-derived quaternary ammonium salts can be coupled with boronic acids under relatively mild conditions. Our optimization has identified ligands that can be used to chemoselectively cross-couple at the ammonium in the presence of chlorides. We demonstrate that intramolecular palladium-catalysed C–H activation is also a viable pathway for the putative benzyl-Pd(II) intermediate obtained upon oxidative addition and have optimised this to obtain fluorene in good yield.

Key words cross-coupling, ammonium salts, palladium catalysis, diarylmethanes, fluorenes

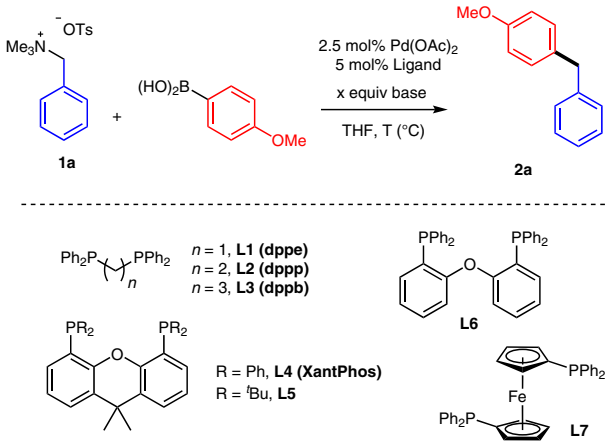
Quaternary ammonium functionality occurs commonly in a wide range of compounds that are used for many applications.[1] It is most frequently employed to promote aqueous solubility or to interact with an anionic partner through ion pairing. It is less often utilised as a reactive functional group, but is nevertheless known to engage in a number of useful reaction types, most prominently in Hofmann elimination[2] and sigmatropic rearrangements such as the Stevens[3] and Sommelet–Hauser[4] rearrangements. Quaternary ammonium salts have also been investigated to a lesser extent in the context of transition-metal-catalysed cross-coupling, where they would represent a useful functional handle for oxidative addition due to their ease of access through simple methylation of amines. Whilst the cross-coupling of aniline-derived ammonium salts has been quite well explored,[5] until recently there have been far fewer methods applicable to benzylaniline-derived ammonium salts. The diarylmethanes that would result from such couplings are a commonly encountered motif in pharmaceuticals and natural products. Very recently a number of elegant nickel-catalysed cross-couplings of benzylamine-derived ammonium salts have been reported with aryl boronic acids to give diarylmethanes,[5g,6] with B_2Pin_2 to give benzylic boronates,[5i,7] and with CO_2 to give carboxylic acids[8] (Scheme 1, a). Notably, Watson and co-workers were able to carry out these couplings stereospecifically from chiral ammonium salts, which proceeded with inversion of configuration.[6,7b] Until our recent work, to our knowledge, only a single example of palladium-catalysed cross-coupling of benzylamine-derived ammonium salts had been reported; that is in a Heck type reaction with alkenes (Scheme 1, b).[9] We recently reported the ion-pair directed C–H borylation of benzylamine-derived quaternary ammonium salts, which delivered high levels of *meta* selectivity by using a novel anionic bipyridine ligand.[10] To probe the elaboration of the ammonium salt products of our borylation reaction, we wished to cross-couple benzylamine-derived ammonium salts with multiple functional handles, including chlorides. Watson and co-workers noted that with their Ni-catalysed method, cross coupling occurred at both the ammonium group and chloride functionality.[6] Accordingly, we sought an alternative method and showed an example of palladium-catalysed coupling of the benzyl ammonium functionality with boronic acids, which allowed us to cross-couple in the presence of the chloride (Scheme 1, c). In the present paper we give a full account of our studies on this reaction (Scheme 1, d).[11] We also disclose the palladium-catalysed C–H activation of an *ortho*-phenyl substituted ammonium salt to form fluorene, which we discovered during the course of these studies (Scheme 1, e).

We chose benzyltrimethylammonium tosylate (**1a**) as our initial optimisation substrate and evaluated a number of ligands using KF as base at 60 °C. Of the ligands surveyed, we found that **L4** (Xantphos), **L6** and XPhos gave the highest yields of product (Table 1, entries 1–12). We subsequently tested **L4** and XPhos at lower temperatures and found that



Scheme 1

Table 1 Optimisation of the Cross-Coupling Reaction on Substrate **1a**



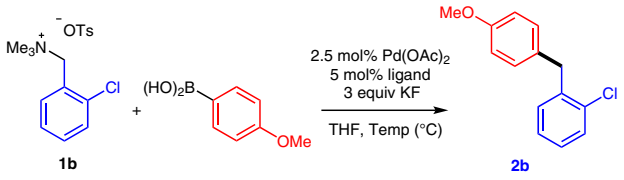
Entry	Ligand	Base	Temp (°C)	Yield **2a** (%)[a]
1	**L1**	KF	60	0
2	**L2**	KF	60	10
3	**L3**	KF	60	63
4	**L4**	KF	60	92
5	**L5**	KF	60	0
6	**L6**	KF	60	93
7	**L7**	KF	60	33
8	XPhos	KF	60	88
9	SPhos	KF	60	85
10	PPh_3	KF	60	29
11	P(*o*Tol)$_3$	KF	60	0
12	(S)-BINAP	KF	60	18
13	**L4**	KF	50	87
14	**L4**	KF	40	47
15	XPhos	KF	50	98 (82)
16	XPhos	KF	40	93
17	XPhos	K_3PO_4	50	94 (82)
18	XPhos	K_2CO_3	50	0
19	XPhos	Na_2CO_3	50	27
20	XPhos	Cs_2CO_3	50	97
21	XPhos	CsOAc	50	33
22	XPhos	CsF	50	93

[a] Determined by ^{1}H NMR analysis with reference to an internal standard. Isolated yield given in parentheses for selected experiments.

XPhos appeared to be the more reactive, still giving good yields at only 40 °C (entries 13–16). A base screen using XPhos at 50 °C revealed that K_3PO_4 is also a highly effective base (entry 17). Among carbonate bases, only Cs_2CO_3 was viable (entries 18–20) and CsF proved to be similar to KF (entry 22).

At this point, we also conducted an investigation into the effect of ligands on the cross coupling of 2-chloro ammonium salt **1b** as we wished to establish a protocol in which chloro-containing substrates could be selectively cross coupled at the ammonium moiety (Table 2). The ability to accomplish this would offer some complementarity to the Ni-catalysed coupling methods in which chloride-containing substrates are incompatible.[6] Our survey revealed that XPhos gives very low yields of the desired product (entry 8), with the majority of coupling occurring at the chloride. However, **L4** (Xantphos), which had been the second most active ligand in optimisation on **1a**, gave no coupling at the chloride and an excellent yield of desired product **2b** (entry 4). In this case, heating to 60 °C was found to be necessary (entry 11). This emphasises how important appropriate ligand choice is to accomplish chemoselectivity in more complex substrates.

Table 2 Optimisation of the Cross-Coupling Reaction on Chloride-Containing Substrate **1b**

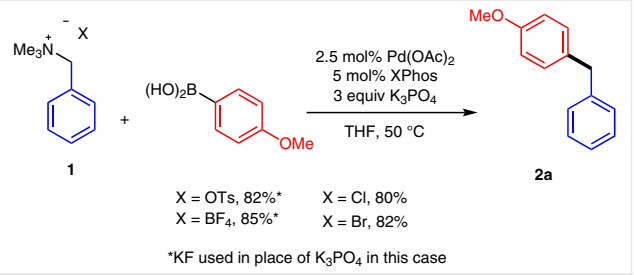


1b 2b

Entry	Ligand	Temp (°C)	Yield **2b** (%)[a]
1	**L1**	60	23
2	**L2**	60	28
3	**L3**	60	87
4	**L4**	60	93 (90)
5	**L5**	60	0
6	**L6**	60	86
7	**L7**	60	55
8	XPhos	60	4
9	SPhos	60	19
10	(*S*)-BINAP	60	5
11	**L4**	50	28

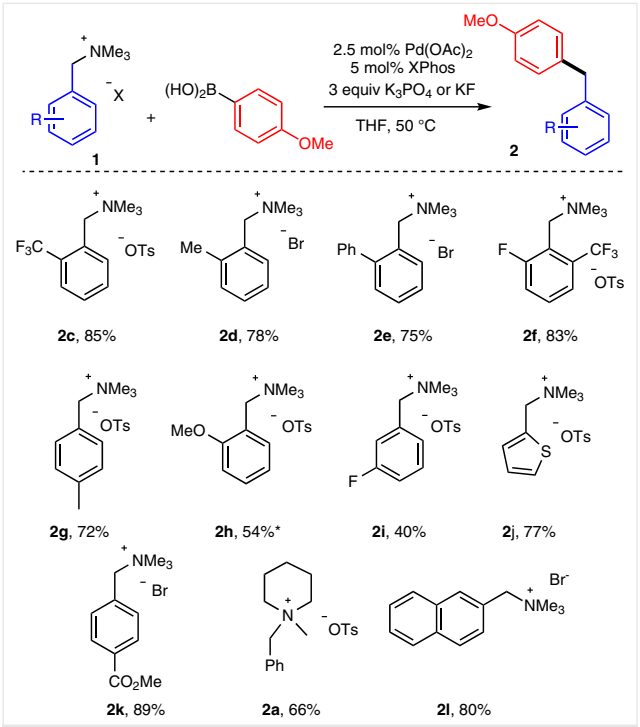
[a] Determined by ^{1}H NMR analysis with reference to an internal standard. Isolated yield given in parentheses for selected experiments.

With optimised conditions in hand on the ammonium tosylate salt **1a**, we sought to examine the tolerance of the counterion of the ammonium salt and were pleased to find the reaction was general, with common counteranions such as halides and tetrafluoroborate all being compatible (Scheme 2).



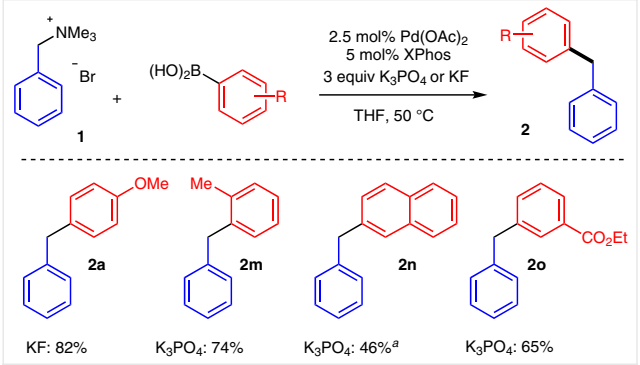
Scheme 2 Evaluation of counteranion of ammonium salt

We next examined the scope of the coupling with respect to the benzylammonium salt component and investigated a range of substituted aromatic and heteroaromatic salts (Scheme 3, starting materials shown in table for clarity). For a selection of examples, we found that *ortho*, *meta* and *para* substitution is tolerated. Furthermore, a heterocyclic thiophene ammonium salt could be coupled in good yield. For the *ortho*-substituted compounds we often found that the bromide salts gave better yields than the corresponding tosylates, suggesting potentially higher reactivity. We also show that the ammonium salt does not have to be a trimethylammonium, as a piperidine variant reacts smoothly. In cases such as **2i**, where the yield was low, the mass balance typically comprised unreacted starting material.

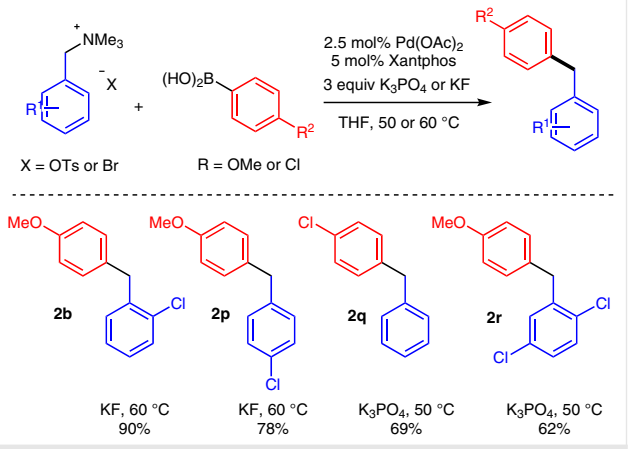


Scheme 3 Scope of the coupling reaction with respect to the ammonium salt

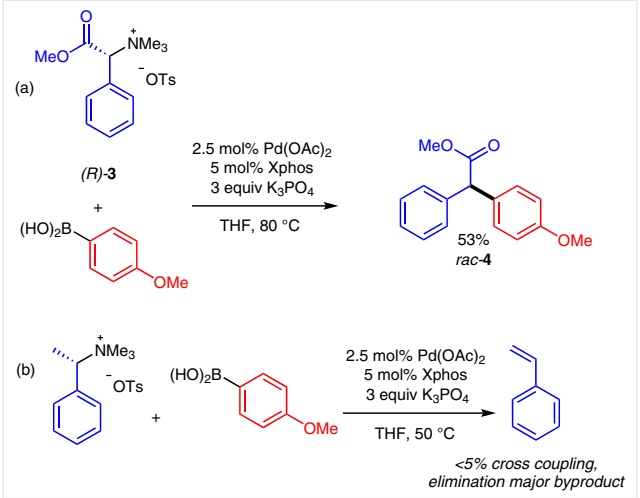
We next demonstrated that a representative selection of boronic acids are compatible in the cross-coupling with benzyltrimethylammonium bromide (Scheme 4). We found that a 4-pyridylboronic acid gave no conversion under these conditions but have not carried out extensive optimisation on this substrate at this stage.



Scheme 4 Selection of boronic acids tested in cross coupling. [a] Comprises an inseparable mixture of 3:1 **2n**/homocoupled boronic acid



Scheme 5 Evaluation of chloride-containing substrates using Xantphos as ligand

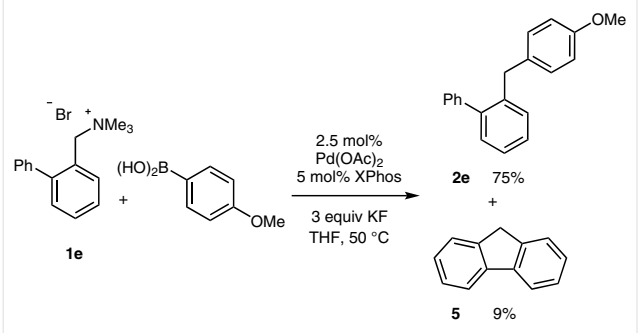


Scheme 6 Evaluation of cross-coupling of an α-chiral ammonium salt under our conditions

We were keen to examine substrates that contain a chloride on either the ammonium salt or the boronic acid to be able to demonstrate orthogonality between the chloride and the ammonium. Based on our previous ligand optimisation (Table 2), we selected Xantphos and found that a number of chloride-containing ammonium salts and a chloride-containing boronic acid give good to excellent yields in the coupling, under mild conditions (Scheme 5). This leaves the chloride functionality intact for further cross-coupling.

Given the elegant work of Watson and co-workers in which stereospecific coupling was found to occur under Nickel catalysis,[6] we were keen to evaluate whether stereochemical information is retained with our palladium-catalysed protocol. By using an elevated temperature of 80 °C, we were able to obtain a moderate yield of coupled product **4** (Scheme 6a). However, HPLC analysis showed that this was racemic. The enantiopurity of the starting ammonium salt **3**, obtained by methylation of phenylglycine methyl ester, was confirmed by ^{1}H NMR analysis after anion exchange with BINPHAT.[12] Therefore, we can conclude that the stereochemical information was lost during the course of the cross-coupling process in this case. Unfortunately, we were not able to obtain more than 5% yield of the corresponding α-methyl substrate under our conditions and thus were not able to determine whether this substrate would retain its stereochemical fidelity (Scheme 6b). In this case, the major by-product was the result of elimination to the styrene and a range of ligands were tested for this substrate with no success.

Finally, in our scope studies, we had observed an interesting side product that was produced in 9% yield in the cross-coupling of 2-phenylbenzylammonium salt **1e** (Scheme 7). This was determined to be fluorene (**5**) and most likely arises through C–H activation onto the *ortho*-phenyl ring being competitive with transmetallation with the boronic acid. Indeed, a literature search revealed that 2-phenylbenzyl halides undergo a similar C–H activation process under Pd(II)-catalysis.[13]

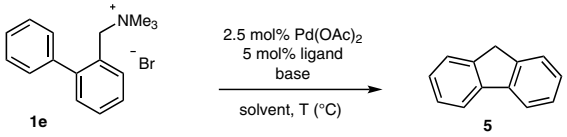


Scheme 7 Fluorene side-product observed in coupling of **1e**

Fluorene derivatives are valuable structural motifs with various applications in chemistry and materials science,[14] and the ability to access them via C–H activation from benzylamine building blocks would be a potentially new and useful route to access them. Furthermore, we have shown in our previous work that it is possible to cross-couple at the *ortho* position in the presence of the benzyl ammonium functionality.[10] This leads to the possibility of a tandem cross-coupling/C–H activation process for fluorene synthesis. In an effort to increase the yield, we undertook optimisation in the absence of the boronic acid (Table 3). Evaluation of bases showed that Cs_2CO_3 is by far the best (entries 1–6), although the yield of fluorene was still only moderate. Reducing the equivalents of base was detrimental (entry 7), as was increasing the temperature to 100 °C (entries 8 and 9). Whilst switching the solvent to dioxane or 1,2-dimethoxyethane (DME) did not significantly improve matters (entries 10–13), it was found that doubling the catalyst/ligand loading was key (entries 14 and 15); the best yield

could be achieved at 90 °C with a moderate three equivalents of base (entry 16). Use of DME as solvent together with (*S*)-BINAP as ligand gave comparable results (entries 17 and 18).[13]

Table 3 Optimisation of Intramolecular C–H Activation to form Fluorine (**5**)



Entry	Ligand	Base (equiv)	Temp (°C)	Solvent	Yield **2a** (%)[a]
1	XPhos	KF (5)	80	THF	0
2	XPhos	NMe_3 (5)	80	THF	0
3	XPhos	K_3PO_4 (5)	80	THF	12
4	XPhos	Na_2CO_3 (5)	80	THF	0
5	XPhos	$NaHCO_3$ (5)	80	THF	0
6	XPhos	Cs_2CO_3 (5)	80	THF	50
7	XPhos	Cs_2CO_3 (2)	80	THF	23
8	XPhos	Cs_2CO_3 (2)	100	THF	8
9	XPhos	Cs_2CO_3 (3)	100	THF	21
10	XPhos	Cs_2CO_3 (2)	100	dioxane	24
11	XPhos	Cs_2CO_3 (3)	100	dioxane	33
12	XPhos	Cs_2CO_3 (3)	100	DME	1
13	(*S*)-BINAP	Cs_2CO_3 (2)	100	DME	35
14[b]	XPhos	Cs_2CO_3 (2)	80	THF	46
15[b]	XPhos	Cs_2CO_3 (2)	90	THF	54
16[b]	XPhos	Cs_2CO_3 (3)	90	THF	64 (41)
17[b]	(*S*)-BINAP	Cs_2CO_3 (2)	90	DME	63 (61)
18[b]	(*S*)-BINAP	Cs_2CO_3 (3)	90	DME	46

[a] Determined by ^{1}H NMR analysis with reference to an internal standard. Isolated yield given in parentheses for selected experiments.
[b] $Pd(OAc)_2$ (5.0 mol%) and ligand (10 mol%) used.

In summary, we have described in detail our studies on the development of the palladium-catalysed coupling of benzyl ammonium salts and boronic acids under mild conditions. We have shown that a variety of substrates are compatible and that, with appropriate ligand choice, chemoselectivity can be obtained between reaction at the ammonium functionality and reaction at a chloride on the arene. This offers an advantage over the related Ni-catalysed processes in which chlorides are not tolerated. In addition, we have found that palladium-catalysed C–H activation can occur if an aromatic ring is present at the *ortho*-position of the benzylammonium salt, demonstrating another productive pathway for the putative benzyl-Pd(II) intermediate other than transmetallation.

All reagents were used as supplied from commercial sources without further purification. Cross-coupling reactions were carried out in 4 mL 15 × 45mm crimp-top vials, which were purged with argon. Vials were heated in welled heating blocks. ^{1}H NMR spectra were recorded with a 600 MHz Bruker Avance 600 BBI spectrometer. Chemical shifts are reported in parts per million (ppm) and the spectra are calibrated to the resonance resulting from incomplete deuteration of solvents. ^{13}C NMR spectra were recorded with a 600 MHz Bruker Avance 600 BBI spectrometer or 500 MHz DCH Cryoprobe spectrometer with complete proton decoupling. Chemical shifts are reported in ppm and calibrated to the solvent resonance resulting from incomplete deuteration. Data are reported as follows: chemical shift in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or combinations of them; ^{13}C signals are singlets unless otherwise stated), coupling constants *J* in Hz, integration (only for ^{1}H spectra). ^{19}F NMR spectra were recorded with a 400 MHz Avance III HD Smart Probe spectrometer. Analytical thin-layer chromatography was performed using precoated Merck glass-backed silica gel plates (Silicagel 60 F254). Visualisation was by ultraviolet fluorescence (254nm) and staining the plates with cerium ammonium molybdate (CAM). Flash column chromatography was performed using silica gel 60 (0.040–0.063 µm).

Synthesis of Ammonium Salts

The preparations of **1a**, **1b**, **1c**, **1d**, **1h** and **1i** were reported previously.[10]

Preparation of Ammonium Tosylate Salts; General Procedure A

A flask was charged with $NaHCO_3$, which was suspended in either MeOH or MeCN. The specified benzylamine was added, followed by methyl toluenesulfonate. After stirring the reaction at r.t. overnight, the solvent was removed and the precipitate was filtered off and washed with CH_2Cl_2. The combined filtrate and washings were concentrated under reduced pressure, redissolved in a minimum amount of CH_2Cl_2 and the product was precipitated by addition of Et_2O. The precipitate was collected by filtration and washed with further Et_2O. If further purification was necessary, it is stated accordingly.

Preparation of Ammonium Bromide Salts; General Procedure B

Trimethylamine was added to a solution of a benzylbromide in MeCN and the resulting mixture was stirred at r.t. for 1 h. The volatiles were evaporated and the remaining precipitate was collected by filtration and washed with Et_2O.

1-([1,1′-Biphenyl]-2-yl)-*N*,*N*,*N*-trimethylmethanaminium Bromide (1e)

Prepared according to General Procedure B with 2-(bromomethyl)-1,1′-biphenyl (0.73 mL, 4 mmol, 1 equiv) and trimethylamine (6 mL, 1 M in THF, 6 mmol, 1.5 equiv) in MeCN (4 mL).

Yield: 1.169 g (3.8 mmol, 95%); white solid.

^{1}H NMR (600 MHz, d_6-DMSO): δ = 7.74 (dd, *J* = 7.7, 1.3 Hz, 1 H), 7.62 (td, *J* = 7.5, 1.4 Hz, 1 H), 7.57–7.44 (m, 4 H), 7.47–7.37 (m, 4 H), 4.68 (s, 2 H), 2.76 (s, 9 H).

^{13}C NMR (151 MHz, d_6-DMSO): δ = 144.55, 139.95, 134.64, 131.48, 130.67, 129.48, 128.87, 127.69, 127.67, 125.35, 64.79, 52.00.

HRMS: *m*/*z* [M]$^+$ calcd for $[C_{16}H_{20}N]^+$: 226.1596; found: 226.1597.

1-(2-Fluoro-6-(trifluoromethyl)phenyl)-*N*,*N*,*N*-trimethylmethanaminium Tosylate (1f)

Trimethylamine (1.28 mL, 5.4 mmol, 4.2 M in ethanol) was added to a solution of 2-fluoro-6-(trifluoromethyl)benzyl bromide (700 mg, 2.72 mmol) in acetonitrile and the solution was stirred at r.t. for 1 h. The volatiles were evaporated under reduced pressure, the residue was dissolved in CH_2Cl_2 and Et_2O was slowly added. The precipitated bromide salt was collected by filtration (840 mg, 2.65 mmol, 98%). This salt (632 mg, 2 mmol) was dissolved in chloroform and AgOTs (837 mmol, 3 mmol) was added. The resulting reaction mixture was stirred for 30 min, then filtered through a bed of Celite. The solvent was removed under reduced pressure to afford the tosylate salt **1f**.

Yield: 572 mg (1.4 mmol, 70%); white solid.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.68–7.63 (m, 3 H), 7.59 (d, *J* = 7.9 Hz, 1 H), 7.43 (t, *J* = 8.8 Hz, 1 H), 7.05 (d, *J* = 8.0 Hz, 2 H), 4.81 (s, 2 H), 3.29 (s, 9 H), 2.25 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.5 (d, $^1J_{C–F}$ = 254 Hz), 143.8, 139.2, 133.9 (d, $^3J_{C–F}$ = 10 Hz), 132.5 (dq, $^3J_{C–F}$/$^2J_{C–F}$ = 1, 32 Hz), 128.6, 125.7, 124.2 (dq, $^4J_{C–F}$/$^3J_{C–F}$ = 6, 3 Hz), 123.0 (q, $^1J_{C–F}$ = 271 Hz), 121.0 (d, $^2J_{C–F}$ = 24 Hz), 113.9 (d, $^2J_{C–F}$ = 16 Hz), 59.6, 54.2, 21.2.

HRMS: *m*/*z* [M]$^+$ calcd for $[C_{11}H_{14}NF_4]^+$: 263.1057; found: 263.1056.

***N*,*N*,*N*-Trimethyl-1-(*p*-tolyl)methanaminium Tosylate (1g)**

To a solution of the corresponding bromide salt (244 mg, 1.0 mmol) in $CHCl_3$ (5 mL) was added AgOTs (418 mg, 1.5 mmol) and the mixture was stirred at r.t. for 30 min. After this time, the mixture was filtered through a thin pad of Celite and the solvent was evaporated to give the title compound.

Yield: 170 mg (0.51 mmol, 51%); white solid.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8.0 Hz, 2 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 7.07 (d, *J* = 8.0 Hz, 2 H), 4.55 (s, 2 H), 3.12 (s, 9 H), 2.30 (s, 3 H), 2.28 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 143.6, 140.5, 139.5, 132.9, 129.6, 128.8, 125.8, 124.7, 68.7, 52.1, 21.28, 21.27.

HRMS: *m*/*z* [M]$^+$ calcd for $[C_{11}H_{18}N]^+$: 164.1434; found: 164.1432.

***N*,*N*,*N*-Trimethyl-1-(thiophen-2-yl)methanaminium Tosylate (1j)**

Prepared according to General Procedure A with thiophen-2-ylmethanamine (0.51 mL, 5.0 mmol, 1 equiv), $NaHCO_3$ (4.2 g, 50 mmol, 10 equiv) and methyl toluenesulfonate (4.7 mL, 25 mmol, 5 equiv) in MeOH (10 mL).

Yield: 1.34 g (4.1 mmol, 82%); white powder.

^{1}H NMR (600 MHz, d_6-DMSO): δ = 7.81 (d, *J* = 5.1 Hz, 1 H), 7.52 (d, *J* = 8.0 Hz, 2 H), 7.40 (d, *J* = 3.2 Hz, 1 H), 7.18 (dd, *J* = 3.7, 5.0 Hz, 1 H), 7.12 (d, *J* = 7.9 Hz, 2 H), 4.81 (s, 2 H), 3.05 (s, 9 H), 2.28 (s, 3 H).

^{13}C NMR (151 MHz, d_6-DMSO): δ = 146.0, 138.2, 134.7, 131.1, 129.4, 128.6, 128.3, 125.9, 62.1, 51.9, 21.2.

HRMS: *m*/*z* [M]$^+$ calcd for $[C_8H_{14}NS]^+$: 156.0841; found: 156.0841.

1-(4-(Methoxycarbonyl)phenyl)-*N*,*N*,*N*-trimethylmethanaminium Bromide (1k)[15]

Prepared according to General Procedure B with methyl 4-(bromomethyl)benzoate (458 mg, 2 mmol, 1 equiv) and trimethylamine (3 mL, 1 M in THF, 3 mmol, 1.5 equiv) in MeCN (8 mL).

Yield: 534 mg (1.9 mmol, 93%); solid.

^{1}H NMR (600 MHz, MeOD-d_4): δ = 8.19–8.14 (m, 2 H), 7.75–7.70 (m, 2 H), 4.65 (s, 2 H), 3.94 (s, 3 H), 3.16 (s, 9 H).

^{13}C NMR (151 MHz, MeOD-d_4): δ = 166.2, 133.0, 132.5, 132.1, 129.7, 68.2, 52.0, 51.6.

Data in agreement with the reported values.[15]

***N*,*N*,*N*-Trimethyl-1-(naphthalen-2-yl)methanaminium Bromide (1l)**[16]

Prepared according to General Procedure B with 2-(bromomethyl)naphthalene (442 mg, 2 mmol, 1 equiv) and trimethylamine (3 mL, 1 M in THF, 3 mmol, 1.5 equiv) in MeCN (4 mL).

Yield: 486 mg (1.7 mmol, 87%); white solid.

^{1}H NMR (600 MHz, MeOD-d_4): δ = 8.15 (s, 1 H), 8.06–7.95 (m, 3 H), 7.66–7.58 (m, 3 H), 4.73 (s, 2 H), 3.18 (s, 9 H).

^{13}C NMR (151 MHz, MeOD-d_4): δ = 134.0, 133.2, 133.0, 128.7, 128.6, 128.1, 127.5, 127.4, 126.7, 125.0, 69.2, 51.9.

Data in agreement with the reported values.[16]

1-(4-Chlorophenyl)-*N*,*N*,*N*-trimethylmethanaminium 4-Methylbenzenesulfonate (1p)

Prepared according to General Procedure A with 4-chlorobenzylamine (0.48 mL, 4.0 mmol, 1 equiv), $NaHCO_3$ (3.36 g, 40 mmol, 10 equiv) and methyl toluenesulfonate (3.0 mL, 20 mmol, 5 equiv) in MeOH (14 mL).

Yield: 1.216 g (3.4 mmol, 85%); white powder.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.0 Hz, 2 H), 7.45 (d, *J* = 8.4 Hz, 2 H), 7.29 (d, *J* = 8.4 Hz, 2 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 4.79 (s, 2 H), 3.22 (s, 9 H), 2.33 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 143.3, 139.8, 136.9, 134.5, 129.3, 128.9, 126.2, 125.7, 67.7, 52.3, 21.3.

HRMS: *m*/*z* [M]$^+$ calcd for $[C_{10}H_{15}NCl]^+$: 184.0888; found: 184.0886.

1-(2,5-Dichlorophenyl)-*N*,*N*,*N*-trimethylmethanaminium Methylbenzenesulfonate (1r)

Prepared according to General Procedure A with 2,5-dichlorobenzylamine (1.0 g, 5.7 mmol, 1 equiv), $NaHCO_3$ (4.7 g, 57 mmol, 10 equiv) and methyl toluenesulfonate (4.3 mL, 28.5 mmol, 5 equiv) in MeOH (20 mL).

Yield: 2.1 g (5.4 mmol, 94%); white powder.

^{1}H NMR (600 MHz, MeOD-d_4): δ = 7.79 (d, *J* = 2.3 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 2 H), 7.63 (d, *J* = 8.5 Hz, 1 H), 7.60 (dd, *J* = 8.5, 2.3 Hz, 1 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 4.71 (s, 2 H), 3.21 (s, 9 H), 2.38 (s, 3 H).

^{13}C NMR (151 MHz, MeOD-d_4): δ = 144.0, 141.9, 136.6, 136.5, 134.8, 134.0, 133.6, 130.1, 129.3, 127.2, 66.4, 54.0, 21.6.

HRMS: *m*/*z* [M]$^+$ calcd for $[C_{10}H_{14}NCl_2]^+$: 218.0498; found: 218.0488.

(*R*)-2-Methoxy-*N*,*N*,*N*-trimethyl-2-oxo-1-phenylethan-1-aminium 4-Methylbenzenesulfonate (3)

Prepared according to General Procedure A with methyl (*R*)-2-amino-2-phenylacetate hydrochloride (807 mg, 4.0 mmol, 1 equiv), $NaHCO_3$ (3.36 g, 40 mmol, 10 equiv) and methyl toluenesulfonate (3 mL, 20 mmol, 5 equiv) in MeCN (14 mL). For further purification, the crude material was dissolved in H_2O (20 mL) and washed with CH_2Cl_2 (3 × 20 mL) and Et_2O (3 × 20 mL). H_2O was removed under reduced pressure, yielding **1p** as an oil (647 mg, 1.7 mmol, 43%). The enantiopurity was determined by dissolving **1p** (5 mg) and *S*-BINPHAT (15 mg) in CH_2Cl_2/acetone (2 mL, 1:1) and stirring for 5 min.

After removing the solvent, the ^{1}H NMR (600 MHz, $CDCl_3$) spectra showed only one ammonium peak, conforming the enantiopurity of the product. A portion (533 mg) of the obtained oil was additionally

washed twice with Et_2O, decanting the washing off and dissolved in a minimum amount of CH_2Cl_2. A white solid (330 mg) was obtained by addition of Et_2O, collected by filtration and washed with Et_2O.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.81–7.76 (m, 2 H), 7.61 (d, *J* = 7.5 Hz, 2 H), 7.55–7.48 (m, 1 H), 7.45 (t, *J* = 7.6 Hz, 2 H), 7.14 (d, *J* = 7.9 Hz, 2 H), 6.09 (s, 1 H), 3.70 (s, 3 H), 3.45 (s, 9 H), 2.32 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.4, 143.3, 139.6, 131.6, 129.7, 128.8, 126.8, 125.9, 74.6, 53.5, 51.8, 21.4.

HRMS: *m*/*z* $[M]^+$ calcd for $[C_{12}H_{18}NO_2]^+$: 208.1338; found: 208.1336.

Palladium-Catalysed Cross-Coupling; General Procedure

The desired amount of substrate, boronic acid (3 equiv), base (3 equiv), $Pd(OAc)_2$ (2.5 mol%) and ligand (5 mol%) were weighed out as solids, the vial was sealed and purged with argon, then solvent was added and the vial was purged again. The reactions were run for 14 h at the specified temperature. The crude material was filtered through a pad of Celite and washed three times with $CHCl_3$. The solvent was removed under reduced pressure, an internal standard was added and the reaction was analysed by ^{1}H NMR spectroscopy. For purification, the analysed mixture was concentrated, the product extracted with Et_2O and filtered through anhydrous $MgSO_4$ and further purified by flash column chromatography.

1-Benzyl-4-methoxybenzene (2a)[17]

Obtained by following the general procedure using **1a** (OTs) (78 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5×10^{-3} mmol), Xphos (4.8 mg, 1×10^{-2} mmol), in THF (0.4 mL) at 50 °C. Purification by silica gel chromatography (20% CH_2Cl_2/petroleum ether) gave **2a**.

Yield: 33 mg (0.16 mmol, 82%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.30 (t, *J* = 7.6 Hz, 2 H), 7.24–7.17 (m, 3 H), 7.13 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 3.94 (s, 2 H), 3.80 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 158.0, 141.7, 133.3, 129.9, 128.9, 128.5, 126.1, 114.0, 55.3, 41.1.

Data in agreement with reported values.[17]

1-Chloro-2-(4-methoxybenzyl)benzene (2b)[18]

Obtained by following the general procedure using 1-(2-chlorophenyl)-*N*,*N*,*N*-trimethylmethanaminium tosylate (36 mg, 0.1 mmol), (4-methoxyphenyl)boronic acid (46 mg, 0.3 mmol), KF (17 mg, 0.3 mmol), $Pd(OAc)_2$ (0.6 mg, 2.5×10^{-3} mmol), Xantphos (2.9 mg, 5×10^{-3} mmol) in THF (0.2 mL) at 60 °C. Purification by silica gel chromatography (25 to 40% CH_2Cl_2/petroleum ether) gave **2b**.

Yield: 21 mg (0.09 mmol, 90%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.37 (dd, *J* = 7.5, 1.7 Hz, 1 H), 7.23–7.10 (m, 5 H), 6.87–6.81 (m, 2 H), 4.05 (s, 2 H), 3.79 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 158.2, 139.2, 134.2, 131.6, 131.0, 130.0, 129.6, 127.6, 126.9, 114.0, 55.3, 38.4.

Data in agreement with reported values.[18]

1-(4-Methoxybenzyl)-2-(trifluoromethyl)benzene (2c)[19]

Obtained by following the general procedure using **1c** (OTs) (78 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), KF (35 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5×10^{-3} mmol), Xphos (4.8 mg, 1×10^{-2} mmol), in THF (0.4 mL) at 50 °C. Purification by silica gel chromatography (20% CH_2Cl_2/petroleum ether) gave **2c**.

Yield: 45 mg (0.17 mmol, 85%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.67 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.43 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.30 (t, *J* = 7.6 Hz, 1 H), 7.18 (d, *J* = 7.8 Hz, 1 H), 7.11–7.06 (m, 2 H), 6.89–6.83 (m, 2 H), 4.14 (s, 2 H), 3.80 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 158.1, 140.0, 131.8, 131.7, 131.5, 130.1, 128.5 (q, $^2J_{C-F}$ = 29.7 Hz), 126.0, 125.7 (q, $^3J_{C-F}$ = 5.8 Hz), 124.5 (q, $^1J_{C-F}$ = 273.9 Hz), 113.9, 55.2, 36.8 (q, $^4J_{C-F}$ = 2.2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –59.6.

Data in agreement with reported values.[19]

1-(4-Methoxybenzyl)-2-methylbenzene (2d)[17]

Obtained by following the general procedure using **1d** (Br) (49 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), KF (35 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5×10^{-3} mmol), Xphos (4.8 mg, 1×10^{-2} mmol) in THF (0.4 mL) at 50 °C. Purification by silica gel chromatography (20%, CH_2Cl_2/petroleum ether) gave **2d**.

Yield: 33 mg (0.16 mmol, 78%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.19–7.12 (m, 3 H), 7.12–7.02 (m, 3 H), 6.85–6.80 (m, 2 H), 3.93 (s, 2 H), 3.79 (s, 3 H), 2.25 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 157.8, 139.3, 136.5, 132.4, 130.2, 129.7, 129.6, 126.3, 125.9, 113.7, 55.2, 38.5, 19.6.

Data in agreement with reported values.[17]

2-(4-Methoxybenzyl)-1,1′-biphenyl (2e)[20]

Obtained by following the general procedure using **1e** (Br) (61 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), KF (35 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5×10^{-3} mmol), Xphos (4.8 mg, 1×10^{-2} mmol) in THF (0.4 mL) at 50 °C. Purification by silica gel chromatography (20%, CH_2Cl_2/petroleum ether) gave **2e**.

Yield: 41 mg (0.15 mmol, 75%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.41–7.35 (m, 2 H), 7.37–7.31 (m, 1 H), 7.34–7.24 (m, 5 H), 7.22 (dd, *J* = 6.7, 1.8 Hz, 1 H), 6.93–6.88 (m, 2 H), 6.80–6.74 (m, 2 H), 3.91 (s, 2 H), 3.78 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 157.7, 142.1, 141.6, 138.6, 133.5, 130.1, 130.0, 129.7, 129.2, 128.0, 127.4, 126.8, 126.0, 113.5, 55.2, 38.1.

Data in agreement with reported values.[20]

1-Fluoro-2-(4-methoxybenzyl)-3-(trifluoromethyl)benzene (2f)

Obtained by following the general procedure using **1f** (OTs) (82 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), KF (35 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5×10^{-3} mmol), Xphos (4.8 mg, 1×10^{-2} mmol) in THF (0.4 mL) at 50 °C. Purification by silica gel chromatography (20%, CH_2Cl_2/petroleum ether) gave **2f**.

Yield: 47 mg (0.17 mmol, 83%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 7.8 Hz, 1 H), 7.38–7.31 (m, 1 H), 7.29–7.22 (m, 1 H), 7.07 (d, *J* = 8.3 Hz, 2 H), 6.84–6.78 (m, 2 H), 4.14 (s, 2 H), 3.77 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.1 (d, $^1J_{C-F}$ = 248 Hz), 158.1, 131.1, 130.9 (dq, $^3J_{C-F}/^2J_{C-F}$ = 4, 30 Hz), 129.2, 128.2 (d, $^3J_{C-F}$ = 9 Hz), 127.3 (d, $^2J_{C-F}$ = 17.6 Hz), 123.9 (dq, $^4J_{C-F}/^1J_{C-F}$ = 4, 274 Hz), 121.9 (dq, $^4J_{C-F}/^3J_{C-F}$ = 4, 6 Hz), 119.3 (d, $^2J_{C-F}$ = 23 Hz), 113.8, 55.3, 30.6 (dq, $^3J_{C-F}/^4J_{C-F}$ = 4, 2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –58.8, –112.3.

HRMS: *m*/*z* $[M]^+$ calcd for $[C_{15}H_{12}F_4O]^+$: 284.0824; found: 284.0823.

1-Methoxy-4-(4-methylbenzyl)benzene (2g)[17]

Obtained by following the general procedure using **1g** (OTs) (67 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5×10^{-3} mmol), Xphos (4.8 mg, 1×10^{-2} mmol) in THF (0.4 mL) at 50 °C. Purification by silica gel chromatography (25%, CH_2Cl_2/petroleum ether) gave **2g**.

Yield: 31 mg (0.14 mmol, 72%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.14–7.06 (m, 6 H), 6.87–6.81 (m, 2 H), 3.90 (s, 2 H), 3.79 (s, 3 H), 2.33 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 158.0, 138.6, 135.5, 133.6, 129.9, 129.2, 128.8, 113.9, 55.3, 40.7, 21.1.

Data in agreement with reported values.[17]

1-Methoxy-2-(4-methoxybenzyl)benzene (2h)[6]

Obtained by following the general procedure using **1h** (OTs) (70 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5×10^{-3} mmol), Xphos (4.8 mg, 1×10^{-2} mmol) in THF (0.4 mL) at 80 °C. Purification by silica gel chromatography (first run with 25% up to 40% CH_2Cl_2/petroleum ether, second run with 10% Et_2O/petroleum ether) gave **2h**.

Yield: 25 mg (0.11 mmol, 54%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.19 (td, *J* = 7.8, 1.8 Hz, 1 H), 7.17–7.11 (m, 2 H), 7.06 (dd, *J* = 7.2, 1.7 Hz, 1 H), 6.91–6.84 (m, 2 H), 6.85–6.79 (m, 2 H), 3.92 (s, 2 H), 3.83 (s, 3 H), 3.78 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 157.8, 157.4, 133.2, 130.2, 130.2, 130.0, 127.4, 120.5, 113.8, 110.5, 55.4, 55.3, 35.0.

Data in agreement with reported values.[6]

1-Fluoro-3-(4-methoxybenzyl)benzene (2i)[17]

Obtained by following the general procedure using **1i** (OTs) (68 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), Pd(OAc)2 (1.1 mg, 5×10^{-3} mmol), Xphos (4.8 mg, 1×10^{-2} mmol) in THF (0.4 mL) at 50 °C. Purification by silica gel chromatography (25%, CH_2Cl_2/petroleum ether) gave **2i**.

Yield: 17 mg (0.08 mmol, 40%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.23 (td, *J* = 7.9, 6.0 Hz, 1 H), 7.13–7.08 (m, 2 H), 6.98–6.93 (m, 1 H), 6.91–6.82 (m, 4 H), 3.92 (s, 2 H), 3.79 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.1 (d, $^1J_{C-F}$ = 245.5 Hz), 158.2, 144.3 (d, $^3J_{C-F}$ = 7.2 Hz), 132.5, 130.0, 129.9 (d, $^3J_{C-F}$ = 8.3 Hz), 124.5 (d, $^4J_{C-F}$ = 2.8 Hz), 115.7 (d, $^2J_{C-F}$ = 21.1 Hz), 114.1, 113.0 (d, $^2J_{C-F}$ = 21.1 Hz), 55.4, 40.88 (d, $^4J_{C-F}$ = 1.8 Hz).

Data in agreement with reported values.[17]

2-(4-Methoxybenzyl)thiophene (2j)[17]

Obtained by following the general procedure using **1j** (OTs) (66 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5×10^{-3} mmol), Xphos (4.8 mg, 1×10^{-2} mmol) in THF (0.4 mL) at 50 °C. Purification by silica gel chromatography (25% up to 40% CH_2Cl_2/petroleum ether) gave **2j**.

Yield: 31 mg (0.15 mmol, 77%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.20–7.17 (m, 2 H), 7.15 (dd, *J* = 5.1, 1.2 Hz, 1 H), 6.93 (dd, *J* = 5.1, 3.4 Hz, 1 H), 6.90–6.84 (m, 2 H), 6.80 (dq, *J* = 3.4, 1.1 Hz, 1 H), 4.12 (s, 2 H), 3.81 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 158.3, 144.8, 132.7, 129.7, 126.9, 124.9, 123.9, 114.0, 55.3, 35.3.

Data in agreement with reported values.[17]

Methyl 4-(4-Methoxybenzyl)benzoate (2k)[21]

Obtained by following the general procedure using **1k** (Br) (58 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), Pd(OAc)2 (1.1 mg, 5×10^{-3} mmol), Xphos (4.8 mg, 1×10^{-2} mmol) in THF (0.4 mL) at 50 °C. Purification by silica gel chromatography (4% up to 8% EtOAc/petroleum ether) gave **2n**.

Yield: 46 mg (0.18 mmol, 89%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.3 Hz, 2 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 7.09 (d, *J* = 8.7 Hz, 2 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 3.97 (s, 2 H), 3.90 (s, 3 H), 3.79 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.2, 158.3, 147.1, 132.3, 130.0, 129.9, 128.9, 128.1, 114.1, 55.4, 52.1, 41.1.

Data in agreement with reported values.[21]

2-(4-Methoxybenzyl)naphthalene (2l)[6]

Obtained by following the general procedure using **1l** (56 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5×10^{-3} mmol), Xphos (4.8 mg, 1×10^{-2} mmol) in THF (0.4 mL) at 50 °C. Analysis of crude ^{1}H NMR showed 82% yield; purification by silica gel chromatography (25%, CH_2Cl_2/petroleum) gave **2l**.

Yield: 40 mg (0.16 mmol, 80%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.85–7.76 (m, 3 H), 7.67–7.63 (m, 1 H), 7.46 (dqd, *J* = 8.2, 6.8, 1.5 Hz, 2 H), 7.34 (dd, *J* = 8.4, 1.8 Hz, 1 H), 7.18 (d, *J* = 8.6 Hz, 2 H), 6.91–6.85 (m, 2 H), 4.12 (s, 2 H), 3.81 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 158.15, 139.19, 133.74, 133.21, 132.18, 130.09, 128.17, 127.74, 127.71, 127.67, 127.03, 126.07, 125.42, 114.04, 55.38, 41.34.

Data in agreement with reported values.[6]

1-Benzyl-2-methylbenzene (2m)[22]

Obtained by following the general procedure using **1a** (OTs) (64 mg, 0.2 mmol), (2-methylphenyl)boronic acid (82 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5×10^{-3} mmol), Xphos (4.8 mg, 1×10^{-2} mmol) in THF (0.4 mL) at 50 °C. Purification by silica gel chromatography (1% up to 3% EtOAc/petroleum ether) gave **2m** (containing ca. 5% homocoupled boronic acid impurity).

Yield: 27 mg (74%); colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.31–7.23 (m, 2 H), 7.22–7.09 (m, 7 H), 4.00 (s, 2 H), 2.26 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 140.5, 139.0, 136.7, 130.4, 130.0, 128.8, 128.5, 126.5, 126.1, 126.0, 39.5, 19.82.

Data in agreement with reported values.[22]

2-Benzylnaphthalene (2n)

Obtained by following the general procedure using **1a** (OTs) (64 mg, 0.2 mmol), naphthalen-2-ylboronic acid (103 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5×10^{-3} mmol), Xphos (4.8 mg, 1×10^{-2} mmol) in THF (0.4 mL) at 50 °C. Purification by silica gel chromatography (2% up to 5% EtOAc/petroleum ether) gave a mixture of **2n** and the homocoupled boronic acid in a 3:1 ratio.

Yield: 28 mg (0.12 mmol, both homo- and cross-coupled products, 46%).

Compound 2l

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.83–7.75 (m, 3 H), 7.65 (d, *J* = 1.8 Hz, 1 H), 7.45 (ddd, *J* = 8.2, 6.8, 1.5 Hz, 2 H), 7.36–7.28 (m, 3 H), 7.28–7.20 (m, 3 H), 4.16 (s, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 141.1, 138.7, 133.7, 132.2, 129.1, 128.6, 128.2, 127.7, 127.7, 127.6, 127.2, 126.2, 126.1, 125.4, 42.2.

Data in agreement with reported values.[6]

Homocoupled Impurity

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 1.7 Hz, 2 H), 7.98 (d, *J* = 8.5 Hz, 2 H), 7.96 (d, *J* = 7.4 Hz, 2 H), 7.91 (dd, *J* = 8.4, 1.8 Hz, 4 H), 7.53 (dqd, *J* = 8.2, 6.9, 1.4 Hz, 4 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 138.5, 133.8, 132.8, 128.6, 128.3, 127.8, 126.5, 126.2, 126.1, 125.8.

Data in agreement with reported values.[23]

Ethyl 3-Benzylbenzoate (2o)[24]

Obtained by following the general procedure using **1a** (OTs) (64 mg, 0.2 mmol), 3-ethoxycarbonylphenylboronic acid (116 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5×10^{-3} mmol), XPhos (4.8 mg, 1×10^{-2} mmol) in THF (0.4 mL) at 50 °C. Purification by silica gel chromatography (5% EtOAc in petroleum ether then a further purification with 30% to 50% CH_2Cl_2/petroleum ether) yielded **2o**.

Yield: 31 mg (0.13 mmol, 65%); colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.93 (br s, 1 H), 7.91 (dt, *J* = 6.9, 1.4 Hz, 1 H), 7.39–7.35 (m, 2 H), 7.31 (t, *J* = 7.6 Hz, 2 H), 7.24–7.20 (m, 3 H), 4.38 (q, *J* = 7.2 Hz, 2 H), 4.05 (s, 2 H), 1.40 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 166.7, 141.4, 140.5, 133.4, 130.7, 130.0, 128.9, 128.6, 128.5, 127.4, 126.3, 60.9, 41.7, 14.3.

Data in agreement with reported values.[24]

1-Chloro-4-(4-methoxybenzyl)benzene (2p)[25]

Obtained by following the general procedure using **1p** (OTs) (36 mg, 0.1 mmol), (4-methoxyphenyl)boronic acid (46 mg, 0.3 mmol), KF (17 mg, 0.3 mmol), $Pd(OAc)_2$ (0.6 mg, 2.5×10^{-3} mmol), Xantphos (2.9 mg, 5×10^{-3} mmol) in THF (0.2 mL) at 60 °C. Purification by silica gel chromatography (25% CH_2Cl_2/petroleum ether) gave **2p**.

Yield: 18 mg (0.08 mmol, 78%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.26–7.21 (m, 2 H), 7.13–7.05 (m, 4 H), 6.86–6.81 (m, 2 H), 3.89 (s, 2 H), 3.79 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 158.2, 140.1, 132.7, 131.9, 130.2, 129.9, 128.6, 114.1, 55.4, 40.4.

Data in agreement with reported values.[25]

1-Benzyl-4-chlorobenzene (2q)[26]

Obtained by following the general procedure using **1a** (Br) (46 mg, 0.2 mmol), (4-chlorophenyl)boronic acid (78 mg, 0.5 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5×10^{-3} mmol), Xantphos (5.8 mg, 1×10^{-2} mmol) in THF (0.4 mL) at 50 °C. Analysis of crude ^{1}H NMR showed 94% yield, purification by silica gel chromatography (1% CH_2Cl_2/hexane) gave **2q**.

Yield: 28 mg (0.14 mmol, 69%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.31 (t, *J* = 7.5 Hz, 2 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.23 (t, *J* = 7.5 Hz, 1 H), 7.18 (d, *J* = 7.5 Hz, 2 H), 7.13 (d, *J* = 8.0 Hz, 2 H), 3.97 (s, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 140.5, 139.6, 131.9, 130.2, 128.8, 128.6, 128.5, 126.3, 41.2.

Data in agreement the reported values.[26]

1,4-Dichloro-2-(4-methoxybenzyl)benzene (2r)

Obtained by following the general procedure using **1r** (OTs) (78 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5×10^{-3} mmol), Xantphos (5.8 mg, 1×10^{-2} mmol) in THF (0.4 mL) at 50 °C. Purification by silica gel chromatography (25% CH_2Cl_2/petroleum ether) gave **2r**.

Yield: 33 mg (0.12 mmol, 62%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.5 Hz, 1 H), 7.16–7.08 (m, 4 H), 6.89–6.83 (m, 2 H), 4.00 (s, 2 H), 3.80 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 158.4, 141.0, 132.7, 132.4, 130.7, 130.6, 130.6, 130.1, 127.7, 114.2, 55.3, 38.3.

HRMS: *m*/*z* [M] calcd for [$C_{14}H_{12}Cl_2O$]: 266.0265; found: 266.0253.

Methyl 2-(4-Methoxyphenyl)-2-phenylacetate (4)[27]

Obtained by following the general procedure using **3** (76 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5×10^{-3} mmol), Xphos (4.8 mg, 1×10^{-2} mmol) in THF (0.4 mL) at 80 °C. Purification by silica gel chromatography (3% up to 5% EtOAc/petroleum ether) gave **5** (27 mg, 0.11 mmol, 53%). Chiral HPLC analysis (Chiralcel OD Column; 1 mL/min; 0.5% *i*PrOH/hexane; t_R = 18.64 min and 19.95 min) of the product showed a racemic mixture was obtained.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 4 H), 7.30–7.21 (m, 3 H), 6.89–6.83 (m, 2 H), 4.99 (s, 1 H), 3.79 (s, 3 H), 3.74 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 173.3, 158.9, 139.1, 130.8, 129.8, 128.7, 128.5, 127.3, 114.1, 56.3, 55.3, 52.4.

Data in agreement with reported values.[27]

Fluorene (5)[28]

Obtained by following the general procedure (excluding boronic acid) using **1e** (61 mg, 0.2 mmol, 1 equiv), Cs_2CO_3 (196 mg, 0.6 mmol, 2 equiv), $Pd(OAc)_2$ (2.2 mg, 1×10^{-2} mmol, 5 mol%), Xphos (9.6 mg, 2×10^{-2} mmol, 10 mol%) in THF (0.4 mL) at 90 °C. Purification by silica gel chromatography (2% CH_2Cl_2/petroleum ether) gave **5**.

Yield: 14 mg (0.08 mmol, 41%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 7.6 Hz, 2 H), 7.56 (d, *J* = 7.4 Hz, 2 H), 7.39 (td, *J* = 7.4, 1.0 Hz, 2 H), 7.32 (td, *J* = 7.4, 1.1 Hz, 2 H), 3.92 (s, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 143.3, 141.8, 126.8, 126.8, 125.1, 120.0, 37.0.

Data in agreement with reported values.[28]

Funding Information

We are grateful to the Engineering and Physical Sciences Research Council (EPSRC, Grant Number EP/N005422/1) and Pfizer for a CASE studentship (H.J.D.), the EPSRC and the Royal Society for a University Research Fellowship (R.J.P.). P.L.T. thanks the Swiss-European Mobility Programme for Traineeships for funding his stay in Cambridge.

Acknowledgment

We thank the EPSRC UK National Mass Spectrometry Facility at Swansea University as well as Professors Steven V. Ley and Matthew J. Gaunt for support and useful discussions. Also thanks to Dr David Blakemore (Pfizer) and Dr Alan D. Brown for useful discussion. We are grateful to Madalina T. Mihai for donation of some ammonium salts used in this study. R.J.P. is very grateful to the organizing committee of the 2016 Bürgenstock conference for a JSP fellowship.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588548.

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